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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,418	11/16/2000	David A. Lewin	10716/12	7715

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SONNENSCHEIN NATH & ROSENTHAL LLP
P.O. BOX 061080
WACKER DRIVE STATION, SEARS TOWER
CHICAGO, IL 60606-1080

EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,418	LEWIN ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-45,47-53 and 55-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-45,47-53 and 55-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 July 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/06/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/06/2004 has been entered.

Claims 42-45, 47-53, 55-69 are pending and being examined.

Claims 42-45, 47-53, 55-69 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants argue that SEQ ID NO: 3 could be used for the detection of misregulation of Wnt-1 pathway. Applicant's arguments have been fully considered but they are not persuasive. Although in the case of Wnt-1 misregulation in the case of Wnt-1 transgenic mice the murine mRNA for SEQ ID NO: 3 may be upregulated, it does not necessarily follow that in case of upregulation of the murine mRNA for SEQ ID NO: 3 Wnt-1 is misregulated because in table 8 it is disclosed that SEQ ID NO: 5 is upregulated in normal tissues as well.

Applicants argue that the correlation between the source of SEQ ID NO: 3 and the elevated expression of its human ortholog (SEQ ID NO: 6) in human cancer cells demonstrates that SEQ ID NO: 3 is useful for the detection of transformed cells, and that

sufficient nexus is described between SEQ ID NO: 3 to a correlated disease condition to provide a credible utility to the skilled artisan. Applicant's arguments have been fully considered but they are not persuasive. The present application doesn't provide any data regarding the expression levels of SEQ ID NO: 6 in cancer cells or normal cells. Furthermore, increased transcript levels are not always correlated with increased protein levels. See Haynes (U), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50-fold. Haynes concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Hancock (V) states that "the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling" (full paragraph 2). Allman (W) indicates that mRNA translation is regulated in many genes and can be mediated by binding of proteins to cis-acting RNA motifs in the untranslated regions of the mRNAs (paragraph bridging pages 5266-5267). Haynes (U), Hancock (V), and Allman (W) provide countervailing evidence that shows that one of ordinary skill in the art would have a legitimate basis to doubt the utility of the claimed mouse polypeptide SEQ ID NO: 3 based on increased transcript levels for the human polynucleotide SEQ ID NO: 5. The skilled artisan would not have appreciated, without more, that increased transcript levels of the human polynucleotide SEQ ID NO: 5 would have suggested a specific and substantial patentable utility for the claimed mouse polypeptide SEQ ID NO: 3. Therefore, increased transcript levels for the human polynucleotide SEQ ID NO: 5 do not impute a specific, substantial, and credible

utility to the human polypeptide SEQ ID NO: 6 or the mouse polypeptide SEQ ID NO: 3. The examiner is not arguing that a correlation does not exist. The examiner is arguing that the present specification fails to disclose what that correlation is or the significance of any such correlation. The specification fails to disclose enough information about the claimed invention (SEQ ID NO: 3) to make its usefulness immediately apparent to those familiar with the technological field of the invention. Accordingly, the assertions that the claimed mouse protein SEQ ID NO: 3 is useful for the detection of transformed cells based on increased transcript levels for the human polynucleotide SEQ ID NO: 5 is not substantial.

The M.P.E.P. reminds Office personnel that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. The examiner has cited Haynes (U), Hancock (V), and Allman (W) as countervailing evidence that that the utilities asserted for the claimed polypeptide (SEQ ID NO: 3) are not substantial because a specific benefit does not exists in currently available form. A specific benefit does not exists in currently available form because the skilled artisan would not know if the expression of the SEQ ID NO: 3 polypeptide would be upregulated, down-regulated, or unchanged in cancer.

Rather than setting a de minimis standard, § 101 requires a utility that is "substantial", i.e., one that provides a specific benefit in currently available form. The examiner accepts for argument's sake that a person skilled in the art could derive some data regarding SEQ ID NO: 3 expression in tumors. The skilled artisan might also be able to derive a practical way of using this data. This further characterization, however,

is part of the act of invention and until it has been undertaken, Applicants' invention is incomplete. In effect, Applicants' position is that the claimed polypeptides are useful because those of skill in the art could experiment with them and figure out for themselves what any observed experimental results might mean. The examiner does not agree that such a disclosure provides a "specific benefit in currently available form." See Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicants argue that from table 8 it is clear to the skilled artisan that SEQ ID NO: 5 is over-expressed and can therefore be used to detect colon, breast and ovarian cancer, and that SEQ ID NO: 3 can be used to detect or treat cancers expressing human orthologs such as SEQ ID NO: 6.. Applicant's arguments have been fully considered but they are not persuasive. While this may be true for SEQ ID NO: 5, the present claims are directed to the mouse polypeptide SEQ ID NO: 3. The present application doesn't provide any data regarding the expression levels of the human polypeptide SEQ ID NO: 6, which is encoded by SEQ ID NO: 5, or the mouse polypeptide SEQ ID NO: 3 in cancer cells or normal cells. Furthermore, increased transcript levels are not always correlated with increased protein levels and the present specification fails to disclose enough information about the claimed invention (SEQ ID NO: 3) to make its usefulness immediately apparent to those familiar with the technological field of the invention, as discussed above.

Applicants argue that SEQ ID NO: 3 can be used to test potential agents that can inhibit over-expression of SEQ ID NO: 3, and that that the skilled artisan would conclude that SEQ ID NO: 3 can be used for the uses described in Applicants response and therefore possess utility. Applicant's arguments have been fully considered but they are not persuasive. In the absence of a patentable utility for the claimed polypeptides, as discussed above, there is no patentable utility for screening for inhibitors of the claimed polypeptide. The utilities disclosed at page 68, lines 14-22 are not specific to the subject matter claimed. Although the specification states that "FCTRX has been implicated in cardiovascular disorders" (page 72, line 11) the specification does not disclose whether FCTRX is up-regulated or down-regulated in cardiovascular disorders, and whether in such disorders FCTRX should be targeted for upregulation or down-regulation. The specification also discloses that "FCTRX ... may also exhibit immune stimulating or immune suppressing activity" (page 74, lines 23-24), and then goes on to list a variety of immune disorders involving immune stimulation or immune suppression. Such a disclosure is not specific. In addition, the present specification discloses that the functions of members of the S100 family of Ca^{2+}-binding proteins are diverse (paragraph bridging pages 11-12). This finding, makes clear that classification of a protein as a S100 family member does not identify it as having a specific function.

Claims 42-45, 47-53, 55-69 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. As

Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

Claims 42-44, 47-52, 55-60, 64, 68, 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that the claims define the claimed genus as related to SEQ ID NO: 3, and that the comparisons of SEQ ID NO: 3 with SEQ ID NO: 6 and with other S100 proteins and calcium binding proteins are adequate and sufficient to define the claimed genus. Applicant's arguments have been fully considered but they are not persuasive.

In addition to reciting a % sequence identity, the claims also recite "the regions corresponding to ... are conserved." The claims do not require that the claimed compounds posses the recited amino acids. The claims only require that "the regions corresponding to" the recited amino acids be "conserved. The specification discloses that the skilled artisan will appreciate that changes can be made to a FCTRX protein without altering the functional ability of the FCTRX protein (page 19, last full paragraph). The specification discloses that:

> "a mutant FCTRX protein can be assayed for (1) the ability to form protein:protein interactions with other FCTRX proteins, other cell-surface proteins, or biologically active portions thereof, (2) complex formation between a mutant FCTRX protein and a FCTRX ligand, (3) the ability of a mutant FCTRX protein to bind to an intracellular target protein or biologically active portion thereof; (e.g. avidin proteins)." Paragraph bridging pages 20-21

In addition, the present specification discloses that the functions of members of the S100 family of Ca^{2+}-binding proteins are diverse (paragraph bridging pages 11-12). This finding, makes clear that classification of a protein as a S100 family member does not identify it as having a specific function.

There is no functional limitation in the claims. In the absence of a functional limitation the claims are construed to encompass any and/or all possible functions. However, the present specification does not identify that regions of an FCTRX protein involved in interactions with other FCTRX proteins or other cell-surface proteins, does not identify any cell-surface protein involved in an interaction with an FCTRX protein, does not identify a FCTRX ligand, and does not identify an intracellular target protein. In view of the absence of a functional limitation in the claims and in view of the potential for binding to undisclosed and unlimited cell-surface proteins, ligands, or intracellular

target proteins, the recitation of a % sequence identity and "the regions corresponding to ... are conserved" does not adequately describe the claimed genus of polypeptides because applicants have not conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, that they were in possession of such undisclosed and unlimited activities of the claimed invention. Furthermore, in view of these potential undisclosed and unlimited activities of the claimed invention, the specification does not clearly allow persons of ordinary skill in the art to recognize that Applicants invented what is claimed.

Claims 42-44, 47-52, 55-60, 64, 68, 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that their arguments in support of utility and written description also support enablement of the claimed invention. Applicant's arguments have been fully considered but they are not persuasive. The specification fails to disclose enough information about the claimed invention (SEQ ID NO: 3) to make its usefulness immediately apparent to those familiar with the technological field of the invention, as discussed above. Applicants have not conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, that they were in possession of such undisclosed and unlimited activities of the claimed invention, as discussed above. Furthermore, in view of these potential undisclosed and unlimited activities of the claimed invention, the

specification does not clearly allow persons of ordinary skill in the art to recognize that Applicants invented what is claimed, as discussed above.

Applicants argue that the comparisons of SEQ ID NO: 3 with SEQ ID NO: 6 and S100 family members, the guidance on sequence identity, and the discussion of sequence variants provides more than adequate guidance to make and use the claimed invention without undue experimentation. Applicant's arguments have been fully considered but they are not persuasive.

In addition to reciting a % sequence identity, the claims also recite "the regions corresponding to ... are conserved." The claims do not require that the claimed compounds posses the recited amino acids. The claims only require that "the regions corresponding to" the recited amino acids be "conserved. The specification discloses that:

> "a mutant FCTRX protein can be assayed for (1) the ability to form protein:protein interactions with other FCTRX proteins, other cell-surface proteins, or biologically active portions thereof, (2) complex formation between a mutant FCTRX protein and a FCTRX ligand, (3) the ability of a mutant FCTRX protein to bind to an intracellular target protein or biologically active portion thereof; (e.g. avidin proteins)." Paragraph bridging pages 20-21

In addition, the present specification discloses that the functions of members of the S100 family of Ca^{2+}-binding proteins are diverse (paragraph bridging pages 11-12). This finding, makes clear that classification of a protein as a S100 family member does not identify it as having a specific function.

There is no functional limitation in the claims. In the absence of a functional limitation the claims are construed to encompass any and/or all possible functions. However, the present specification does not identify that regions of an FCTRX protein

involved in interactions with other FCTRX proteins or other cell-surface proteins, does not identify any cell-surface protein involved in an interaction with an FCTRX protein, does not identify a FCTRX ligand, and does not identify an intracellular target protein. The skilled artisan is left to an extensive amount of random, trial and error experimentation wherein SEQ ID NO: 3 is mutated and assayed for binding to undisclosed and unlimited cell-surface proteins, ligands, or intracellular target proteins. Such extensive, random, trial and error experimentation is considered undue. There are no working examples of an FCTRX protein interacting with other FCTRX proteins or with other cell-surface proteins. There are no working examples of a FCTRX ligand. There are no working examples of an FCTRX protein binding to an intracellular target protein. The examiner is aware that working examples are not required. However, they are a factor to be considered. The first paragraph of 35 U.S.C. 112 requires that the scope of the claims bear a reasonable correlation to scope of enablement provided by specification; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. The presence specification provides no guidance that would allow the skilled artisan to predict which cell-surface proteins, ligands, or intracellular target proteins would interact with a mutant FCTRX protein, and provides no guidance to predict which amino acid residues are involved in any such interactions. It is this additional characterization that is required

in order to obtain the functional and structural data needed to make and use the claimed invention that constitutes undue experimentation. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them then the instant application does not support the breadth of the claims. In the instant case the present specification does not provide the guidance needed to predictably alter SEQ ID NO: 3, such it would interact or bind an undisclosed and unlimited cell-surface protein, ligand, or intracellular target protein.

New Formal Matters, Objections, and/or Rejections:

The application is not fully in compliance with the sequence rules, 37 C.F.R. § 1.821-1.825. The application cannot issue until it is in compliance. Figure 7 discloses "SEQ ID NO: 49." However, the sequence listing does not disclose "SEQ ID NO: 49." The sequences in figure 4B-4E labeled as SEQ ID NO: 3, SEQ ID NO: 39, SEQ ID NO: 40, or SEQ ID NO: 6 do not correspond to SEQ ID NO: 3, SEQ ID NO: 39, SEQ ID NO: 40, or SEQ ID NO: 6 in the sequence listing.

Correction is required.

The drawings were received on 07/06/2004. These drawings are not acceptable.

In addition to Replacement Sheets containing the corrected drawing figure(s), applicant is required to submit a marked-up copy of each Replacement Sheet including

annotations indicating the changes made to the previous version. The marked-up copy must be clearly labeled as "Annotated Marked-up Drawings" and must be presented in the amendment or remarks section that explains the change(s) to the drawings. See 37 CFR 1.121(d). Failure to timely submit the proposed drawing and marked-up copy will result in the abandonment of the application.

Claim Rejections - 35 USC § 112

Claims 42-44, 47-52, 55-60, 64, 68, 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are claiming one or more subgenera of conserved residues or regions. Support for these subgenera of conserved residues or regions corresponding to the recited amino acids cannot be found in the disclosure as originally filed. This lack of support raises the issue of new matter.

Claims 42-44, 47-52, 55-60, 64, 68, 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 42-44, 47-52, 55-60, 64, 68, 69 are indefinite over the recitation of "the regions corresponding to ... conserved."

It is unclear if the phrase "regions corresponding to" should be interpreted narrowly to encompass only materials that have a structure identical to the recited amino acids or if the phrase should be interpreted broadly to encompass materials which have a

region "similar" to the recited amino acids. In the case of the latter, the nature and extent of the "correspondence" is unclear. The metes and bounds are not clearly set forth.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571)272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306
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FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
SEPTEMBER 17, 2004